UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

mv

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/433,418	11/04/1999	JOEL B. EPSTEIN	8105-013-US	2559

32301 7590 03/09/2007
CATALYST LAW GROUP, APC
9710 SCRANTON ROAD, SUITE S-170
SAN DIEGO, CA 92121

EXAMINER	
HUI, SAN MING R	
ART UNIT	PAPER NUMBER
1617	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/433,418	EPSTEIN, JOEL B.	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,6,9-11,19-21,23,24 and 27-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6,9-11,19-21,23,24 and 27-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 7, 2006 has been entered.

Claims 1-3, 5-6, 9-11, 19-21, 23-24, and 27-29 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19-21, 23-24, and 27-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In the instant case, the instant specification does not reasonably provide enablement for methods of preventing graft-versus-host disease of the mouth.

Ex parte Forman (230 USPQ 546, BdPatApp & Int.) and *In re Wands* (858 F.2d 731, 8 USPQ2d 1400, 1404, Fed. Cir. 1988) provide several factors in determining whether the specification of an application allows the skilled artisan to practice the invention without undue experimentation. Having said factors in mind, the instant specification fails to reasonably provide enablement for methods of preventing the claimed condition. Specifically, the recitation of "preventing graft-versus-host disease of the mouth" in the instant claim 19, direct the claims to methods of preventing a pathological condition. However, the specification fails to properly enable such methods.

In the instant case, the burden of enabling for preventing graft-versus-host disease of the mouth requires appropriate screening testing, subsequent data compilation, and finally appropriate data analysis, to assess and properly enable one skill in the art whether graft-versus-host disease of the mouth are prevented from formation in a patient. For example, the specification must provide adequate guidance whether graft-versus-host disease of the mouth can be prevented from forming in a patient once the azathiopine or its metabolites is administered to a subject susceptible to develop graft-versus-host disease of the mouth.

Moreover, the specification must provide direct evidence associating the claimed prevention to the composition applied. The burden of showing preventative properties is greater than that of enabling a treatment, because one of ordinary skill in the art must not only show competent screening of those subjects susceptible to such conditions, but also show that the efficacy of a preventative method is directly caused by applying or administering the instantly claimed composition to the susceptible subjects.

In this case, there is no teachings for screening methods identifying susceptible subjects nor is there any direct evidence of efficacy establishing a preventative property associated with the claimed composition. Furthermore, the state of the prior art concerning methods of preventing graft-versus-host disease of the mouth is not well described, nor does it provide for any absolute prevention. Accordingly, undue experimentation is necessary to determine screening and testing protocols to demonstrate the efficacy of the presently claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11 and 29 are depending from claims 1 and 19, wherein the composition employed in claims 1 and 19 can only have azathiopine or its metabolites and pharmaceutical carriers, and nothing else since claims 1 and 19 recite the transitional phrase "consisting of". Claims 11 and 29 recite "further comprising..." which renders the claims indefinite as to the composition makeup of the composition recited. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5-6, 9-11, 19-21, 23-24, and 27-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hewitt et al. (USPN 5,540,931), Lozada, and Sharpe et al. (USPN 5,637,616) in view of Batt et al. (USPN 5,578,609).

Hewitt et al. (USPN 5,540,931) teaches topical compositions for site-specific immune suppression comprising one or more immunosuppressants, e.g., azathioprinse, cyclophosphamide, didemnin B, deoxyspergualin. Methotrexate, thalidomide, or combinations thereof, see claims 1-7. Hewitt et al. also teaches the employment of hydrocortisone in its formulation, see claims7-9. Hewitt finally teaches that some conditions may require topical immunosuppresion alone, see col. 9, lines 19-21 for example.

Lozada teaches a method of treating patients with chronic inflammatory mucocutaneous disease having oral ulcerations including lichen planus, pemphigus vulgaris and bullous pemphigoid comprising administering azathioprine (an immunosuppressive agent), and a steroidal antiinflammatory agent see page 257 first full paragraph, see also MATERIALS AND METHODS. Lozada teaches that Azathioprine is administered from 5 mg every other day to 100 mg/day, see pages 258 Drugs and Results. See also page 259, Col. 2, first full paragraph as well as page 258 Adverse effects.

Sharpe et al. (USPN 5,637,616) teaches a method for topical treatment of mucosal lesions and in particular bullous pemphigoid, lichen planus, and aphthous ulcers employing gel, ointment, cream, foam, lotion or a solution that is orally applied, swished and expectorated or swallowed, see in particular claims 5-13. Sharpe et al. (USPN 5,637,616) also teaches that topical corticosteroids are known to be employed in treating aphthous ulcers, see col. 4, lines 41-47. Sharpe et al. (USPN 5,637,616) also teaches that bullous pemphigoid is known to be treated with immunosuppressive agents in addition to steroids and pemphigus is known to be treated with corticosteroids, such as prednisone and prednisolone as well as immunosupressive agents such as azathioprine, cyclosphamide, methotrexate and cyclosporine, see col. 3, lines 23-30; see also col. 2, 62-col. 3, line 4. Sharpe et al. also teaches the employment of anti-inflammatory agents in its composition, see in particular col. 10 lines 51-56. Finally, Sharpe et al. teaches that these oral lesions are accompanied by pain, see col 1, lines 39-43, see also col. 5, lines 32-36.

Hewitt, Lozada and Sharpe et al. (USPN 5,637,616) taken together, do not particularly teach the incorporation of NSAIDS in their methods. The primary references do not expressly teach the active agents being swished in the mouth. The primary references do not expressly teach the use of azathiopine alone in the method of treating graft-versus-host disease of mouth.

Batt et al. teaches a method of treating graft versus host disease employing immunosuppressants such as azathioprine and steroids with combination of NSAID such as aspirin, ibuprofen and naproxen (See col. 7, lines 4-44).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ a liquid formulation comprising azathioprine (an immunosuppressive agent), corticosteroids, and NSAID or azathiopine alone in the herein claimed method of treating autoimmune diseases of the mouth. It would have also been obvious to employ NSAIDS in their method.

One of ordinary skill in the art would have been motivated to employ a liquid formulation comprising azathioprine (an immunosuppressive agent), corticosteroids, and NSAID in the herein claimed method of treating autoimmune diseases of the mouth because these agents individually are known to be useful in treating autoimmune diseases of the mouth. Combining two or more agents which are known to be useful to in treating autoimmune disease of the mouth individually into a single composition useful for the very same purpose is prima facie obvious (See *In re Kerkhoven* 205 USPQ 1069). In addition, even selecting only one immunosuppressants from what the prior arts disclosed in the method of treating graft-versus-host disease of mouth is still considered obvious since the cited prior arts clearly disclosing the use of various immunosuppressants useful topically with or without swallowing to treat graft-versus-host disease of mouth. The general principle is that immunosuppressants are being useful and effective in treating graft-versus-host disease of mouth. Therefore, employing any known immunosuppressant, including azathiopine, would be reasonably expected to be useful in the method of treating graft-versus-host disease of mouth. Examiner notes that the claims, as written, actually read on the combination of agents since the dependent claims further comprising secondary therapeutic agents into the

method. Furthermore, the oral lesions symptomatic of autoimmune diseases of the mouth are known to be painful. The skilled artisan would have been motivated to add NSAIDS to formulations known to be useful in treating autoimmune diseases of the mouth because pain is known to be associated with these oral lesions. Optimization of amounts is within the purview of the skilled artisan and is therefore obvious. In addition, swishing the active in the mouth would be considered an alternative method to deliver the active in contact with the oral lesion. One of ordinary skilled in the art is in possession of conventional method of delivering active to the disease site. Therefore, absent evidence to the contrary, swishing the active in order for the active agents got in contact with the disease site would be considered an obvious alternative to one of ordinary skill in the art.

Response to Arguments

Applicant's arguments filed August 7, 2006 averring the cited prior arts' failure to teach not using azathiopine alone and always required a combination have been fully considered but they are not persuasive. Examiner believes the new reasoning set forth above had addressed the arguments. In summary, the instant claims actually read on the combination of immunosuppressant. Furthermore, taking the references together, one of ordinary skill in the art would immediately realize that various immunosuppressants, alone or in combination, as useful in treating graft-versus-host disease of the mouth. Therefore, it would be reasonably expected the employment of

any known immunosuppressants, including azathiopine alone, would be sufficient to treat graft-versus-host disease of the mouth.

Applicant's arguments filed August 6, 2006 averring the Examiner using hindsight reasoning have been considered, but are not found persuasive. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, there are several references pointing towards the fact that various immunosuppressants as useful in treating graft-versus-host disease of the mouth; and thus, it is obvious to employ any known immunosuppressants, including azathiopine alone or in combination, to treat graft-versus-host disease of the mouth.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (571) 272-0626. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (571) 272-0629. The fax

phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

San-ming Hui
Primary Examiner
Art Unit 1617